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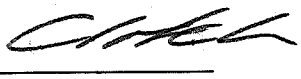

For and on behalf of RWS Group Ltd

The 7th day of January 2008

19 **FEDERAL REPUBLIC OF GERMANY**

[crest]

**GERMAN PATENT AND TRADEMARK OFFICE**

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56 Literature considered in assessing the patentability:

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DE 27 20 194 A1
US 41 62 318 A
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WO 99/13 884 A1

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**The following details have been taken from the documents submitted by the Applicant**

54 Use of triazoline derivatives

57 Use of a triazoline derivative or a pharmaceutically acceptable salt thereof for the treatment of Parkinson's disease

Published specification

# Use of triazolinone derivatives

## Use of a triazolinone derivative or a pharmaceutically acceptable salt thereof for the treatment of Parkinson's disease

## Description

The present invention relates to the use of triazolinone derivatives for the treatment of Parkinson's disease.

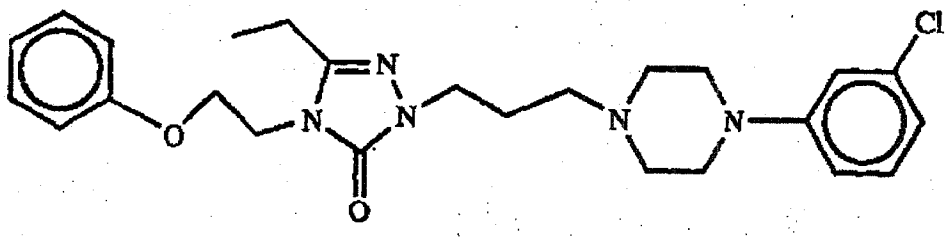
Parkinson's disease is associated with breakdown of nerve cells in the brain which are required to produce so-called dopamine. Dopamine is one of the messengers in the brain enabling information exchange between neighboring nerve cells. The decline in dopamine in parkinsonian patients means that other messengers predominate, in other words the equilibrium ratio of the messengers is disturbed. During the chronic disease, the messenger concentrations become grossly unbalanced. The symptoms of Parkinson's disease include, in particular, difficulties of coordination and impairments of mobility.

In most cases, the disease has its onset only at an advanced age, in particular between about the ages of 60 and 70. In rarer cases, however, the disease onset is also considerably earlier, in some circumstances even before the age of 30. It is estimated that more than one million patients in the world suffer from Parkinson's disease. One problem is that the disease is often not diagnosed in the early stage. Many patients are therefore not treated to begin with.

One of the conventional treatment methods is to replace the missing messenger dopamine by addition of appropriate medicaments. One problem with this is that on prolonged intake of L-dopa its activity declines so that the dosage must be increased. However, high L-dopa dosages lead to a number of side effects and, on prolonged intake, to undesired late sequelae. This is a problem in particular for those patients in whom the disease becomes manifest at a comparatively young age. A high percentage of patients treated with L-dopa shows motor impairments after only a few years. For these reasons, there has recently been an increasing trend to employ, especially at the start of therapy, so-called dopamine agonists which are then in part combined with L-dopa in advanced stages of the disease.

Nefazodone, a phenoxyethyltriazolinone-phenylpiperazine, has become known as antidepressant in the art. It is assumed that the antidepressant effect of nefazodone is connected with the advancement of the serotonergic activity in the central nervous system. Nefazodone hydrochloride is ordinarily used as active substance in the corresponding medicaments. This agent is employed exclusively for depressive disorders. The manufacturer indicates some side effects in the information for use, it being indicated inter alia that relatively common side effects occurring which affect the nervous system are impairments of the coordination of movements (ataxia) and slowing of movements. The skilled worker concludes from this that nefazodone is contraindicated for the treatment of Parkinson's disease with which, after all, the aforementioned symptoms inter alia occur. The skilled worker thus had no reason to test the efficacy of nefazodone for the treatment of Parkinson's disease. The applicant is accordingly unaware of corresponding investigations in this direction.

The exact formula of nefazodone is represented for example in DE 34 43 820 C2 and corresponds to structural formula I indicated below



I

**Nefazodone**

The exact name according to chemical nomenclature is 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-4-(2-phenoxyethyl)-2H-1,2,4-triazol-3(4H)-one. In the aforementioned publication, nefazodone is referred to as agent having antidepressant activity. No further indications are mentioned.

Owing to the abovementioned fact, that the dopamine usage of parkinsonian patients increases after a prolonged treatment time, together with the increase in unwanted side effects and the occurrence of long-term damage, and in view of the wide distribution of the disease, whose incidence is moreover apparently increasing, there is a great national economic need to find medicaments which make possible a therapy in which the L-dopamine doses to be administered can be reduced. The object of the present invention is accordingly to provide a composition which reduces the dopamine usage of parkinsonian patients, displays good efficacy for the treatment of the pathological symptoms and moreover shows minimal or only insignificant side effects.

The solution to this object is provided by the inventive use with the features of the main claim. Inventively it is envisioned that a phenylpiperazine derivative be used to treat Parkinson's disease. Particularly suitable in the context of the present

invention is a triazolinine-phenylpiperazine and/or a derivative thereof. Particular preference is given to using phenoxyethyl-triazolinone-phenylpiperazines (nefazodone) or a phenoxyethyl-triazolinone-phenylpiperazine (nefazodone) or a pharmaceutically acceptable salt thereof, an example being nefazodone hydrochloride.

Investigations for the purposes of the present invention have shown that intake of the aforementioned inventive substances by parkinsonian patients surprisingly leads to a considerable reduction in the dopamine usage. It was possible to show in some patients that parkinsonian patients regularly taking L-dopamine are able to reduce very considerably their dopamine usage compared with formerly on simultaneous intake of nefazodone. The dopamine dose necessary on additional intake of nefazodone can in many cases be reduced for example to one half or even one third of the dose previously necessary on treatment with dopamine alone. Moreover, according to the invention there is not only a reduction in the daily dose of dopamine, but remarkably the intake of nefazodone also improves the time distribution of the dopamine which has been taken in the patient's body. Dopamine usually has a relatively short half-life in the human body, so that its effect does not persist for very long. With pure dopamine therapy, therefore, the parkinsonian patient must take the dopamine distributed relatively frequently over the day, for example at an interval of two to two and a half hours. Since the effect of dopamine is additionally impaired by simultaneous intake of food, it is recommended that no food be consumed for a period after its intake. This leads to a considerable impairment of the quality of life of parkinsonian patients, especially when the disease is already in an advanced stage and therefore high dosages of dopamine and relatively frequent intake at short

intervals of time is necessary. The inventive use in particular of nefazodone or derivatives thereof in patients who take dopamine at the same time by contrast advantageously leads to the effect of dopamine being distributed in time. Evidently, for a reason which is as yet unknown, a depot effect arises, with which the dopamine in the patient's body is released more slowly owing to the intake of nefazodone. It is thus possible for dopamine intake to take place not only in lower doses but also at larger intervals in time.

It was additionally established that the inventive use of, in particular, nefazodone and derivatives thereof leads to a reduction in the side effects associated with conventional Parkinson's medicaments comprising dopamine. For example, one unpleasant side effect of dopamine, namely the occurrence of uncontrolled motor activity in the patient, is positively influenced by nefazodone.

A further advantage of the inventive use of nefazodone is that it can easily be administered orally, especially in tablet form, in contrast to other anti-Parkinson's medicaments which have been disclosed recently and which have to be injected and, in some cases, can be injected only by the physician if the syringe must be placed for example in the head region in the direct vicinity of the brain region.

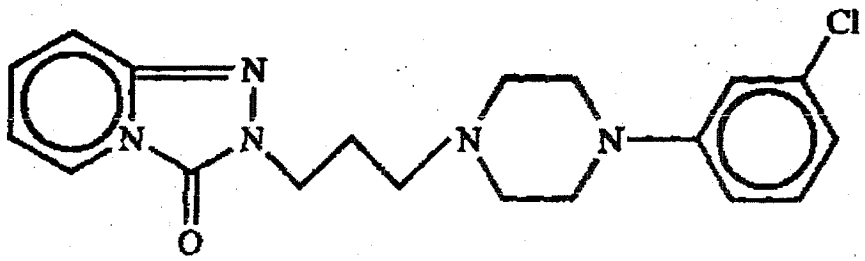
If the active substance of the invention is administered in tablet form, such a tablet normally comprises conventional excipients besides the active substance itself. Examples of suitable excipients are those used for the commercially available medicament "Nefadar®", and these are in particular microcrystalline cellulose, povidone, poly(O-carboxymethyl)starch, sodium salt, highly disperse

silicon dioxide, magnesium stearate, iron oxide or the like.

In addition, nefazodone or the usual medicament-compatible salts thereof is generally well tolerated and shows only relatively few or rare serious side effects.

A preferred dosage for the purposes of the present invention comprises daily intake of a few 100 mg, this intake preferably being distributed over the day in a plurality of doses, preferably through intake of tablets. The tablets normally comprise the active substance in an amount of 100 mg or 200 mg. A preferred daily dosage is, for example, in the range from about 300 to 600 mg in a day, so that this can be administered by intake two to three times a day in single doses of 100 mg or 200 mg. For example, if a total dose of 500 mg a day is intended, it is possible to take 200 mg in the morning, 200 mg at midday and 100 mg in the evening. The inventive administration of the nefazodone product led to it being possible considerably to reduce the dopamine usage of the patient. For example, it was possible to reduce the daily dose necessary for a patient whose disease was already in an advanced stage from the 900 mg to 1000 mg of dopamine a day before the inventive treatment with nefazodone to a total daily dose of only 300 to 400 mg, in other words to about one third. Intake of L-dopamine was possible in considerably smaller single doses and simultaneously with a greater interval in time, for example in three single doses of about 125 mg, which were taken for example three times a day, specifically in the morning, at midday and in the evening. This had the considerable advantage for the patient that, because of the larger interval in time of L-dopamine intake, it was possible to take meals undisturbed in a usual rhythm as for a healthy person.

Besides nefazodone, an active substance suitable for the inventive use is in particular another triazolone which likewise comprises as substituent a phenylpiperazine group which is linked via a propyl group to a nitrogen atom of the triazolone ring. It is the 1,2,4-triazolo[4,3-a]pyridine which has become known under the name trazodone and is described in U.S. Pat. No. 4,338,317 as antidepressant. The structural formula II of trazodone is represented below.




II

The exact name according to chemical nomenclature is 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-1,2,4-triazolo[4,3-a]pyridin-3(2H)-one.

It is to be assumed that the triazolinone group which is present in both trazodone and in the abovementioned nefazodone, and the substituents which exhibit a plurality of agreements in both cases, namely the propylphenylpiperazinyl group on the one hand and the substituents in position 4 and 5 of the triazole ring on the other hand, are responsible for the inventive effect on Parkinson's disease. The exact mechanism of action has not yet been investigated.

Investigations for the purposes of the present invention have shown that additional intake of caffeine, for example in tablet form, assists the mentioned positive effect of nefazodone and can lead to a further reduction in the dopamine usage of the patient. It is recommended in this connection for example to take a single dose of about 50 mg to about

0.2 g of caffeine in tablet form. Caffeine tablets with this active substance dose are commercially available. It has additionally been established that intake of acetylsalicylic acids can also assist the mentioned positive effects of nefazodone, so that supplementary therapy with acetylsalicylic acid may also be advisable. An appropriate example is intake of acetylsalicylic acid in tablet form with single doses of, for example, 500 mg per tablet. Combinations of caffeine and acetylsalicylic acid active substances in one tablet are also possible, resulting in the advantage that the patient has to take only one medicament.

**Claims**

1. The use of a triazolinone derivative or of a pharmaceutically acceptable salt thereof for the treatment of Parkinson's disease.

2. The use of a triazolinone containing at least one phenylpiperazine substituent connected optionally via an alkyl group to the triazole ring or of a derivative thereof or its pharmaceutically acceptable salt for the treatment of Parkinson's disease.

3. The use of 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-4-(2-phenoxyethyl)-2H-1,2,4-triazol-3 (4H)-one (nefazodone) or of a pharmaceutically acceptable salt thereof for the treatment of Parkinson's disease.

4. The use as claimed in claim 3 in patients simultaneously treated with L-dopamine.

5. The use as claimed in claim 3 or 4, characterized in that a daily dose totaling between about 100 mg and about 800 mg, where appropriate in a plurality of single doses, is administered to the patient.

6. The use as claimed in any of the preceding claims, characterized in that a daily dose of between about 300 and about 600 mg is administered to the patient.

7. The use as claimed in any of the preceding claims, characterized in that the phenylpiperazine derivative, in particular the nefazodone or its pharmaceutically acceptable salt is administered in two to three single doses.

8. The use as claimed in any of the preceding claims, characterized in that the phenylpiperazine derivative, in particular the nefazodone or its pharmaceutically acceptable salt is administered in one or more single doses each of about 100 mg to about 200 mg.

9. The use as claimed in any of the preceding claims, characterized in that the phenylpiperazine derivative, in particular the nefazodone or its pharmaceutically acceptable salt is administered in tablet form intended for oral intake.

10. The use as claimed in any of the preceding claims, in conjunction with intake of a caffeine and/or acetylsalicylic acid-containing composition in the same period for the treatment of Parkinson's disease.